REMARKS

Status of the Claims

Claims 9-10 and 15-33 remain in the case. Claims 1-8 and 11-14 are cancelled. Claim 9 has been amended herein. Support for the amendments can be found in previous claim 9 and original claim 1.

Claims 15-33 are new. Support for dependent claims 15-17 and 25-27 (reciting specific dosages) may be found in original claims 4-6. Support for dependent claims 18 and 28 may be found at page 14, lines 10-12 of the application as filed. Support for dependent claims 19-21 and 29-31 (reciting specific devices, namely a catheter and a stent) may be found at page 6, line 16 in Example 1, page 15, line 24 in Example 2 (for the catheter) and at page 24, lines 26-27 (for the stent) of the application as filed. Support for dependent claim 24 may be found in previous claim 9. Support for claims 22-23 and 32-33, specifying that delivery may be made following or during PTCA, may be found in Examples 1 and 2, at page 24, lines 26-29 of the application as filed.

Objection to Priority and Specification

Applicants respectfully submit this objection has been overcome by the appropriate amendment to the specification. As amended, the specification clearly recites the cross-reference to the related applications, showing that the present application is a continuation of parent application U.S. Serial No. 10/088,405.

Rejections Under 35 USC §112, First Paragraph

Applicants submit that this rejection has been overcome by the appropriate amendments to the claims. Specifically, claims 9-14 were rejected as allegedly containing subject matter not described in the specification as originally filed. As amended, Applicants submit this objection is rendered moot. Accordingly, Applicants respectfully request that the rejection under 35 USC §112, first paragraph, be withdrawn.

Rejections Under 35 USC §103(a)

Claim 9 was rejected as being obvious over the article entitled "17Beta-Estradiol Inhibits Proliferation and Migration of Human Vascular Smooth Muscle Cells by Dai-Do et

al., Cardiovascular Research 32 (1996) 980-985 (Dai-Do). However, Applicants respectfully traverse the rejection because Dai-Do does not teach the use of 17-β estradiol *in vitro*.

As amended, the current claims recite a method of applying 17-β estradiol at the injured site in the lumen of a blood vessel. In contrast, Dai-Do describes the effect of 17-β estradiol on smooth muscle cells (SMC) ***in vitro***. *In vitro* observation of SMC proliferation and migration inhibition by 17-β estradiol is not predictive of the latter compound's ability to reduce restenosis at an injured site *in vivo*. A person of ordinary skill in the art knows that many factors absent in an *in vitro* model of SMCs proliferation and migration come into play in *in vivo* experiments. Such factors could constitute obstacles to the success of the candidate compound in reducing restenosis in the blood vessel of an animal. Indeed, at the time of filing, other therapeutic agents known to inhibit SMC proliferation *in vitro* have later been shown to be unsuccessful in *in vivo* experiments. For instance, an antisense oligonucleotide targeting proliferating cell nuclear antigen which appeared of interest as an anti-restenosis agent in view of preliminary *in vitro* results was shown to be unsuccessful in *in vivo* experiments (see page 82, right-hand column, first paragraph of Kipshidze *et al.* submitted herewith as Exhibit A). Similarly, a bolus injection of phosphorotioate oligomers was shown to be unsuccessful in primate models (see page 83, right-hand column, first paragraph of Kipshidze *et al.* submitted herewith). Therefore, at the time of filing, there was no reasonable expectation in light of Dai-Do that *in situ* administration of 17-β estradiol in an animal would successfully reduce restenosis.

Claims 9-14 were further rejected as being unpatentable over U.S. Patent No 5,866,561 to Ungs (Ungs). More particularly, the Examiner indicates that at column 1, lines 40-50, Ungs states that it has been suggested to apply estrogen to a stenosed region after PTCA to prevent restenosis. The Examiner further alleges that Ungs "clearly teaches that 17-beta-estradiol is effective in reducing restenosis."

Applicant respectfully disagrees because Ungs does not provide data to support the conclusion that administering estrogen at the dilated region after PTCA has been "suggested" to prevent restenosis. Ungs appears to base its conclusion (lines 45-50) on the teachings of U.S. Patent No 5,376,652 to Javitt (Javitt). Javitt teaches the use of 27-hydroxycholesterol to inhibit restenosis. While Javitt mentions that it might be useful to employ known activators of 27-hydroxycholesterol such as estrogen to reduce restenosis through the action of 27-hydroxycholesterol, it provides no data to further support this proposal. Hence, Ungs cannot

be cited as "clearly teach(ing) that 17-beta-estradiol is effective in reducing restenosis" as the Examiner claims. Further, while Javitt may be viewed as providing an incentive to test the ability of estrogen to prevent restenosis, Javitt provides no reasonable likelihood of success. Therefore, Applicants submit that one of skill in the art could not predict that 17-β estradiol would be a successful inhibitor of restenosis when applied at an injured site of a vessel.

It is also respectfully submitted that the presently claimed invention differs from what Ungs itself discloses in at least two important aspects. 1) Ungs does not disclose administration of 17-β estradiol at the injured site of a vessel; and 2) Ungs does not disclose administration of 17-β estradiol for reducing restenosis.

Ungs discloses the application of estrogen to the blood vessel walls at a treatment site proximal to or upstream of stenosis. Ungs teaches applying estrogen to the blood vessel walls at a treatment site proximal to or upstream of stenosis as an alternative means to increase perfusion when PTCA is impracticable (see col. 1, lines 52-64 of Ungs). Therefore, the method taught in Ungs is useful when PTCA may not be performed because the stenosed region is not accessible (see col. 2, lines 9-15 of Ungs). Accordingly, Ungs teaches applying estradiol to an uninjured site on a blood vessel to promote generation of other vessels or to increase permeability so that more blood can reach ischemic tissue. See, for instance, the abstract, of the field of the invention at col. 1, line 5 and col. 2, lines 6-7 of Ungs.

Further, Ungs is silent regarding using estradiol to increase reendothelization and vascular function at an injured site. Although Ungs appears to recognize that it is useful to promote endothelial cell growth after injury, vascular endothelial growth factor (VEGF) is the only agent discussed as being suitable for such a purpose (see col. 1, lines 30-34 of Ungs). The use of estradiol to promote and increase reendothelization and vascular function is not discussed. Further still, as noted above, Ungs is not directed towards the repair of injured blood vessels. Rather, Ungs is directed to a method of promoting the generation of new vessels and to increase blood permeability. In short, Ungs does not provide any working examples suggesting the estradiol is useful for promoting angiogenesis, let alone useful in repairing blood vessels.

It is respectfully submitted that none of the cited references, either alone or in combination, disclose or suggest that estradiol can be administered at an injured site of a vessel to improve reendothelization and vascular endothelial function.

CONCLUSION

It is submitted that the application is in condition for allowance. Favorable reconsideration is respectfully requested.

Other than the extension fee, additional fees are not believed to be needed for this amendment. However, if additional fees are needed, please charge them to Deposit Account No. 17-0055.

Respectfully submitted,

Baskaran Chandrasekar, et al.

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By: Ann E Rabe

Ann E. Rabe
Registration No. 56,697
Quarles and Brady LLP
411 East Wisconsin Ave.
Milwaukee, WI 53202
(414) 277-5613

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